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ARTICLE TYPE

Fe/Al pillared clay catalyzed solvent-free synthesis of bisindolylmethanes using diversly substituted indoles and carbonyl compounds

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A fast, solvent free solid acid mediated synthetic strategy for the synthesis of bisindolylmethanes has been developed. The 10 process is applicable to a wide range of substrate with different protecting group survival properties. Reusability of Fe/Al pillared clay for more than 5 cycles without significant loss of catalytic activity adds to the features of the reaction.

The most ubiquitous of the known bioactive alkaloids are based ¹⁵ on the indole moiety. Particularly bis(indolyl)alkanes widely occur in various natural products isolated from marine sponge alkaloids.¹ Diindolylmethanes (DIMs) and related compounds exhibit a wide range of biological activities including antibacterial and antitumor.² In a programme directed towards the ²⁰ synthesis of indole based new chemical entities, in our earlier communication, we designed synthesis of N,N'-glycoside derivatives of DIM's for their antiproliferative potential against various cancer cell lines.³ Owing to their unprecedented role in biological chemistry, development of new catalytic processes for ²⁵ the generation of DIM's is always welcomed in organic chemistry.

Synthetic strategies mediated through protic acids⁴ and Lewis acids (BF₃, AlCl₃),⁵ ionic liquids,⁶ ion exchange resin⁷ and rare earth metal⁸ have been reported in the literature for the ³⁰ preparation of bis(indolyl)methanes. However use of harsh conditions, long reaction times in several cases, limited substrate scope and above all generation of harmful wastes are some of the problems associated with existing methodologies. In some cases use of microwave and ultrasonic irradiation have been used to

³⁵ circumvent the problems, however, problems arise when large scale production is needed. Thus, development of new, efficient and eco-friendly catalysts for the synthesis of bis(indolyl)methanes is still needed. In recent years, solid acid catalysts have evolved as potential candidates for organic 40 synthesis. Easy separation of product from reaction mixtures,

efficiency in submolar scale and reusability are some of the advantages of these catalysts over the conventional homogeneous ⁵⁰ catalysts.⁹⁻¹² Despite the fact that solid acid catalysts like zeolites,¹³ clays¹⁴ and surface modified zirconia¹⁵ are well reported for DIM preparation, longer reaction time and use of toxic and volatile organic solvents as reaction media still demand the need of new catalyst to fill the void between catalysis and ⁵⁵ green chemistry. With our recent success in the development of solid catalysts and their applications in organic synthesis,^{16,17} herein, we disclose the preparation and application of Fe/Al pillared clay catalysts for the rapid synthesis of bis(indolyl) methanes.

⁶⁰ Fe/Al pillared clay catalysts were prepared by impregnation method. FeCl₃ and AlCl₃ diluted in distilled ethanol, stirred vigorously for one hour and then H⁺ form of Montmorillonite K-10 clay added to the solution and stirred and refluxed for 15h under N₂ atomosphere and then dried under vacuum. Considering

65 on acidity, samples were further calcined at different temperatures to get three different forms of catalyst (Table 1) and stored in vacuum desiccators.

Surface properties of the catalysts were determined by X-ray powder diffraction (Fig. 1) and ammonia-TPD (Fig. 2 and 3). The ⁷⁰ calcination temperature greatly affects the performance and the physico-chemical properties of the catalyst, as determined by XRD studies. The XRD results are presented in Fig. 1. The phases were identified by search match procedure with the help of DIFFRACPLUS software using JCPDS databank. The ⁷⁵ Montmorilonite (**M**) peak at 2θ = 19.600° is the peak for 001 plane which shows the pillaring effect. **CAT-2** (Fe/Al pillared clay-250°C) has Chloraluminite phase (**F**, Fig. 1) and the TPD (Fig. 2) results show that a desorption peak have appeared around 350°C which may be responsible for presence of Chloraluminite ⁸⁰ phase. As per the XRD, the iron and aluminum species in **CAT-3**

do not have their independent phase and it is most probable that Fe and Al have been hosted in the Montmorilonite phase. Although phases were generated for **CAT-1** (Fe/Al pillared clav-

 110° C) but was not stable as found to be highly hygroscopic and so found difficult to handle. So we further continue our work with

CAT-2 (Fe/Al pillared clay-250°C) and **CAT-3** (Fe/Al pillared clay-425°C) as they are thermally robust and stable at room

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temperature.

Prior to Ammonia-TPD studies, samples were preheated at 250 $^{\circ}$ C for 2 h in a flow of pure nitrogen (99.9%), then cooled to room temperature. After the pretreatment, the samples were saturated

- ⁵ with 10% anhydrous ammonia gas until saturated adsorption. The temperature was increased to 80 °C and kept there for 2 h to remove the physisorbed ammonia. Finally the system was heated from 80 °C to 1200 °C at the rate of 10 °C/min and the desorbed gas was monitored with a T.C.D. detector. All the flow rates were maintained at normal temperature and pressure (NTP).
- Ammonia-TPD results revealed three temperature maximums for the samples, **CAT-2** (Fe/Al pillared clay-250 °C) and **CAT-3** (Fe/Al pillared clay-425°C) indicating the presence of three



¹⁵ Fig. 1. CAT-1 (Fe/Al pillared clay-110 °C): M, Q; CAT-2 (Fe/Al pillared clay-250 °C): M, Q, F; CAT-3 (Fe/Al pillared clay-425°C): M, Q.

M: Montmorillonite, Q: Quartz, F: Chloraluminite (AlCl₃.6H₂O)

different types of acids sites with different acid strength distribution. The total amount of ammonia desorbed in case of the ²⁰ sample heated at 425 °C is much higher than that of sample heated at 250 °C (Fig. 2 and 3, Table 1, entries 2 and 3). It clearly



Fig. 2 Ammonia desorption curve of CAT-2 (Fe/Al pillared clay-250 °C)



25 Fig. 3 Ammonia desorption curve of CAT-3 (Fe/Al pillared clay-425 °C)

indicates that calcinations at high temperature show a strong influence on the acidic properties of the Fe-Al pillared clay and also stability.

To check the catalytic activity of Fe/Al pillared clay catalysts, in ³⁰ a model reaction of 4-hydroxybenzaldehyde (1equiv.) with 5bromoindole (2 equiv.) in the presence 0.5 mol % of catalysts was used at room temperature with acetonitrile as solvent to yield **3a** as the sole product (Scheme 1). The yield of product was determined after 20 min. by HPLC and results are summerized in ³⁵ Table 1. **CAT-3** (Fe/Al pillared clay-425 °C) was found to be an effective exterior and the electrophilic substitution exercises of

effective catalyst for the electrophilic substitution reaction of indole with aldehydes giving bis(indolyl)methanes **3a** in excellent yields as shown in Table 1. It clearly indicates that as the ammonia desorption value increases, the yield of the product also ⁴⁰ goes up.



Scheme 1 Condensation of 5-bromoindole with 4-hydroxybenzaldehyde using CAT-2 and CAT-3.

45 Table 1 Effect of ammonia desorption value of catalysts on the yield of product for the reaction of 5-bromoindole and 4-hydroxybenzaldehyde using acetonitrile as solvent.

Entry	Catalyst	Strength of Site/	NH ₃	BET	Yield
		Peak temps (C)/	desor-	surface	%
		Temp. range	bed	area,	
			(µmol	(m^2g^{-1})	
			/g)		
1	CAT-1	n.d. ^a	n.d. ^a	n.d. ^a	n.d.ª
	(Fe/Al				
	pillared clay-				
	110°C)				
2	CAT-2	Weak/ 207/ 40-	395	142	87
	(Fe/Al	400			
	nillared clay-				
	250 °C)				
		Medium/ 580/	186		
		400-630			
		Strong/ 682/ 630-	201		
		1000	-01		
3	CAT-3	Weak/ 105/ 40-	1486	156	91
•	(Fe/Al	360			
	nillared clay	500			
	A25°C				
	425 C)	Madium/ 404/	1222		
		2(0, 595	1322		
		360-585			
		Strong/ 627/ 585-	793		
		1000			

^an.d.: not determined

The efficacy of the **CAT-3** was checked in different organic solvents and it was found the acetonitrile is best in terms of yield ⁵⁰ and reaction time. The progress of the reaction was monitored in solvent free conditions as well and to our delight the reaction proceeded smoothly leading to the formation of the desired product in >93 % yield (Table 2, entry 8, Scheme 2) making the process more environmentally viable.

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Entry	Solvent	Time (hr)	Yield ^a %
1	CUCN	0.20	01
2	AcOFt	0.20	91 87
3	CH ₂ Cl ₂	1	84
4	MeOH	1	81
5	EtOH	1.30	78
6	DMF	2	78
7	THF	2.45	60
8	Solvent free ^b	0.15	94

^a Yield determined through HPLC

^b Indole (2 equiv.), 4-hydroxy benzaldehyde (1 equiv.), Cat-3 (0.5mol%), 90°C

5 The catalyst could be separated from the reaction mixture by dissolving the product in dichloromethane, filtering, washing with dichloromethane, and drying at 120 °C. Reusability of the catalyst was checked for several times and product 3a was obtained in good to excellent yields with substantial (>15%) loss 10 of activity after more than five cycles Fig. 4.



Fig. 4 Effect of reusability of Fe/Al pillared clay catalyst on the yield of product 3a.

To check the substrate scope of the reaction, various aldehydes 15 including aliphatic (Table 3, entries 1j, 10-1p and 3c-3d) and, aromatic (Table 3, entries 1a-1i, 1k-1n, 2b and 3a-3b), having both electron withdrawing (Table 3, entries 11-1n and 3b) and electron donating (Table 3, entries 1d-1h) were reacted with

Table 3 Synthesis of DIMs by condensations of indoles and carbonyl 20 compounds catalyzed by CAT-3(Fe/Al pillared clay-425 °C) via Scheme 2



Scheme 2 Condensation of substituted indoles with different carbonyl
compound using CAT-3 (Fe/Al-pillared clay-425 °C).

1a-1p , $R_2 = X = H$,	2a-2b , X = H,
$1a, R_1 = phenyl, R_2 = X = H, 96\%$	$2a$, $R_1 = CH_3$, $R_2 = CH_3$, 86%
1b , $R_1 = 4$ -OH-phenyl, 95%	2b , R_1 = Phenyl, R_2 =CH ₃ , 81%
1c , R_1 = 3-OH-phenyl, 93%	$3a-3d$, $R_2 = H$, $X = Br$
³⁰ 1d , R ₁ =4-OMe-phenyl, 92%	3a , $R_1 = 4$ -OH-phenyl, 95%

	1. R = 2.2 (OM-) should 010/	View Article Online 2b $P = 4 Pr r h area 020/$
	1e, $K_1 = 2,3$ -(OMe) ₂ -pnenyl, 91%	30 , $R_1 = 4$ -Br-phenyl, 93%
	1f, R ₁ =2,4-(OMe) ₂ -phenyl, 88%	$3c, R_1 = n-C_3H_7, 89\%$
	1g , R ₁ =3,4-(OMe) ₂ -phenyl, 90%	3d , $R_1 = n - C_7 H_{15}$, 86%
	1h , R ₁ =2,5-(OMe) ₂ -phenyl, 87%	
35	1i, R ₁ =4-NMe ₂ -phenyl, 88%	
	1j, R_1 = cyclohexyl, 84%	
	1k , $R_1 = 2$ -naphthyl, 87%	
	11 , $R_1 = 4$ -Cl-phenyl, 95%	
	$1m, R_1 = 4$ -Br-phenyl, 94%	
40	1n , R ₁ =4-NO ₂ -phenyl, 92%	
	10 , $R_1 = n - C_3 H_7$, 85%	
	$1\mathbf{p}, \mathbf{R}_1 = \mathbf{n} \cdot \mathbf{C}_7 \mathbf{H}_{15}, 80\%$	

^a Characterized through spectroscopic analysis.

^b % HPLC yield.

45 substituted indoles at 90 °C in absence of organic solvent in an oil bath for 10-30 min. In all cases the corresponding DIM derivatives were obtained in good to excellent yield. (Table 3).

Table 4 Synthesis of DIMs by condensations of diversly substituted indoles and carbonyl compounds catalyzed by CAT-3 (Fe/Al pillared 50 clay-425 °C) via Scheme 3.

Indole	Carbonyl compound	Compound ^a	Yield %
Br N	F CHO	Br N (4a)	87
Br (5)	F CHO		89
Br AcO OAc OAc (6)	CHO	$ \begin{array}{c} & \\ Br \\ & \\ & \\ AcO \\ & \\ AcO \\ & \\ QAc \\ \\ \\ QAc \\ \\ \\ QAc \\ \\ \\ QAc \\ \\ \\ \\ QAc \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	88
Br N N N N	F CHO	$ \begin{array}{c} Br \\ N \\ $	87
	F CHO	$ \begin{array}{c} & & \\ & & $	89

^a Compound characterize through spectroscopical analysis.

^b Isolated yield after column chromatography. ^c% HPLC yield: 85-94%

In general aldehydes with electron withdrawing groups react faster than their counter ones. Compared to aldehydes, ketones 55 reacted in much sluggish manner and best conversions for the

25

products (2a-2b) were obtained after 20 min with a 1:2:0.5 ratios of ketone/ indole/CAT-3.

To check the applicability of this catalyst in synthesis of various N-substituted DIM's, N-alkylated,¹⁸ N-benzylated,¹⁸ N-⁵ glucoside³, N-triazole¹⁹ and N-sulphonyl¹⁸ derivatives of indole were allowed to react with carbonyl compound under standardised reaction conditions (Scheme 3) to yield the corresponding DIM derivatives (Table 4).



Scheme 3 Condensation of N-substituted indoles with carbonyl compound using CAT-3 (Fe/Al-pillared clay-425 °C).

Finally a comparison was made between various known catalyst and our newly synthesised catalyst (Table 5). It was found that 15 catalytic efficiency of our catalyst is superior to other one in terms of catalyst loading and reaction time.

Table 5. Comparison of the catalytic efficiency of Fe/Al pillared clay with various reported catalyst for reaction of indole with benzaldehyde.

Entry	ReactionCondition/ Time	Catalyst content	Yield %	Ref.
1	Zeokarb-225/CH ₃ CN 7.5 h	0.5 g	95	11
2	ZrO ₂ (400°C) 1h	-	70	15
3	ZrOCl ₂ .8H ₂ O, Solvent- free, 50 °C 40min.	5mol%	84	12
4	SO ₄ ⁻² /ZrO ₂ (500°C) 50min.	1.5 N	89	15
5	PO ₄ - ³ /ZrO ₂ (500°C) 20min.	1.5 N	92	15
6	Fe/Al pillared clay (425°C)/solvent free, 15min.	0.5 mol%	94	

20 Conclusions

In conclusion, we have developed an efficient synthetic protocol for the synthesis of BIMs from various aldehydes and diversly substituted indoles using 0.5 mol% Fe/Al pillared clay as a catalyst. Key features of the protocol include mild reaction

25 conditions, reduced reaction times, high yields and wide substrate scope. Above all the recyclability of the catalyst for more than 5 cycles without significant loss in catalytic activity adds to the merits of the process.

30 Experimental

All chemicals and reagents required for the reactions were procured from Sigma-Aldrich with purity 98% and used without further purification. The products were characterized using ¹H NMR, ¹³C NMR spectra. NMR spectra of the products were 35 obtained using Bruker 200,400 and 500 MHz spectrometers with

TMS as the internal standard. Column chromatography was performed on silica gel, Merck grade 60-120 mesh size. TLC was performed on 0.25 mm E. Merck precoated silica gel plates (60 F254). % Purity of the samples were measured by HPLC(Agilent

40 1260 infinity). The compounds (1a-3d, 6a and 7a) are already well known in the literature.^{3-11, 20}

Preparation of catalyst: Fe/Al pillared clay catalysts were prepared by impregnation method. anhydrous FeCl₃ (1g, 6.17 mmol) and AlCl₃ (1g, 7.49 mmol) diluted in distilled ethanol (90

45 mL), stirred vigorously for one hour and then H⁺ form of Montmorillonite K-10 clay (2g) was added to the solution, stirred with reflux for 15h under N2 atomosphere and then dried under vacuum. Considering on acidity, samples were further calcined at different temperatures to get three different forms of catalyst 50 (Table 1) and stored in vacuum desiccators.

General procedure for synthesis of compounds from 1a-8a A mixture of aldehyde or ketone (1 equiv.), indole (2 equiv.) and CAT-3 (0.5 mol%) in test tube was heated with stirring at 90°C for the appropriate time 10-30 min. After cooling, 55 dichloromethane was added to the reaction mixture, filtered and washed (2x20 mL) to recover the catalyst. The filtrate was purified by column chromatography (ethylacetate: petroleum

ether/3:7) to afford the pure product. HPLC Method: purity of the samples 1a-3d were measured by

60 and 4a-8a were measured by HPLC methods A and B, respectively. Complete description of both HPLC methods are given in supporting information.

Spectral data of selected compounds

- **Compound 3a**: ¹H NMR (500MHz, CDCl₃): δ 5.68 (s, 1H), 6.63 65 (s, 2H), 6.77 (d, J=8.5Hz, 2H), 7.13 (d, J = 8.5Hz, 2H), 7.23 (d, J = 8.7, 2H, 7.25 (d, J = 8.7Hz, 2H), 7.47 (s, 2H) ; ¹³C NMR (CDCl₃): 154.13, 135.3, 129.6, 128.6, 124.9, 124.7, 124.5, 122.3, 119.2, 115.2, 112.6, 112.5, 39.04; MS m/z (M⁺+Na): 519. HPLC method A, retention time: 34.254, Peak area: 95%.
- ⁷⁰ Compond 3b: ¹H NMR (200MHz, CDCl₃): δ 5.70 (s, 1H), 6.62 (s, 2H), 7.13-7.28 (m, 8H), 7.45 (s, 2H), 8.07 (s, 2NH); ¹³C NMR (CDCl₃): 141.6, 135.3, 132.2, 129.8, 128.0, 125.1, 124.8, 122.1, 118.5, 112.7, 112.7, 39.3; MS m/z (M⁺+Na): 582.7. HPLC method A, retention time: 37.551, Peak area: 93%.
- ⁷⁵ Compound 3c: ¹H NMR (200MHz, CDCl₃): δ 0.95 (t, J=7.2, 7.4, 3H), 1.22-1.44 (m, 2H), 2.05-2.15 (m, 2H), 4.34 (t, J = 7.3 Hz, 7.5 Hz, 1H), 6.82 (s, 2H), 7.16-7.26 (m, 4H), 7.65 (s, 2H), 8.19 (s, 2NH); ¹³C NMR (CDCl₃): 135.2, 128.6, 124.6, 122.6, 122.0, 119.6, 112.5, 112.3, 37.5, 33.7, 21.3, 14.1; MS m/z (M⁺+Na):
- 80 469.1. HPLC method A, retention time: 36.552, Peak area: 89%. **Compound 3d:** ¹H NMR (200MHz, CDCl₃): δ 0.83-0.86 (m, 3H), 1.23-1.34 (m, 10H), 2.1-2.3 (m, 2H), 4.32 (t, J = 7.5 Hz, 1H), 6.92 (s, 2H), 7.21-7.26 (m, 4H), 7.65 (s, 2H), 7.98 (s, 2NH); ¹³C NMR (CDCl₃): 135.2, 128.6,124.6, 122.6, 122.0, 119.6,
- 85 112.5, 112.3, 35.2, 33.9, 31.8, 29.6, 29.3, 28.2, 22.6, 14.1; MS m/z (M⁺+Na): 525.7. HPLC method A, retention time: 39.268, Peak area: 86%.

Compound 4a: ¹H NMR (400MHz, CDCl₃): δ 0.85 (t, J = 8 Hz,3H), 1.21-1.31 (m, 8H), 1.72-1.76 (m, 4H), 3.98 (t, J = 8 Hz,

- 90 1H), 5.71 (s, 1H), 6.49 (s, 2H), 6.98 (t, J = 8Hz, 2H), 7.17-7.23 (m, 6H), 7.42(s, 2H); ¹³C NMR (CDCl₃): 139.2, 135.4, 129.9, 129.8, 128.9, 128.3, 124.3, 122.3, 117.2, 115.4, 115, 112.1, 110.9, 46.4, 39.1, 29.8, 28.9, 22.2, 13.9; MS m/z (M⁺+Na): 659.9. HPLC method **B**, retention time: 4.139, Peak area: 94%.
- 95 Compound 5a: ¹H NMR (400MHz, CDCl₃): δ 5.14 (s, 4H), 5.76 (s, 1H), 6.56 (s, 2H), 6.88 (m, 4H), 7.00-7.05 (m, 4H), 7.20-7.25 (m, 4H), 7.43-7.45 (m, 6H); ¹³C NMR (CDCl₃): 136.1, 135.6,

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132, 129.9, 129.8, 129.1, 128.7, 128.0, 125.0, 122.5, 121.6, 118.0, 115.4, 115.2, 112.8, 111.3, 49.6, 39.3; MS m/z (M⁺+Na): 857.7. HPLC method **B**, retention time: 4.160, Peak area: 91%. **Compound 6a:** ¹H NMR (400 MHz, CDCl₃): δ 1.51, 1.55, 1.92, 5 1.94, 1.97, 1.98, 1.99, 2.04(8s, 24H, CH₃CO), 3.8-3.9 (m, 2H), 4.09-4.16 (m, 4H), 5.1-5.2 (m, 2H), 5.3-5.4 (m, 6H), 5.6 (s,1H),

- 6.6, 6.7 (d, J = 7.2Hz, 2H),7.08 (d, J = 8.4Hz, 2H), 7.20 (d, J = 8.4, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.28 (m, 5H), 7.4 (s, 1H). ¹³C NMR (CDCl₃): 169.1, 168.4, 167.5, 167.4, 140.4, 134.3, ¹²⁴ L 121.5, 129.7, 129.6, 129.4, 127.7, 125.1, 124.6, 122.0
- ¹⁰ 134.1, 131.5, 128.7, 128.6, 128.4, 127.7, 125.1, 124.6, 123.9, 121.4, 121.2, 118.7, 118.1, 112.8, 112.7, 110.8,110.5, 82.9, 82.5, 73.8, 73.7, 71.9, 71.8, 69.9, 69.3, 67.0, 60.9, 60.7, 37.6, 19.7, 19.6, 19.53, 19.50, 19.4, 19.0, 18.9. MS m/z(M⁺+Na):1195.1. HPLC method **B**, retention time:11.880, Peak area: 88%.
- ¹⁵ **Compound 8a:** ¹H NMR (400MHz, CDCl₃): δ 5.45 (s, 1H), 6.85 (s, 2H), 7.05-7.18 (m, 8H), 7.25 (d, J = 4Hz), 7.45 (dd, J = 4Hz, 4Hz), 7.71-7.74 (m, 4H), 7.85 (s, 1H), 7.88 (s, 1H); ¹³C NMR (CDCl₃): 166.9, 164.8, 163.1, 161.1,134.9, 134.8, 134.3, 133.4, 131.3, 129.7, 129.5, 129.4, 126.2, 123.8, 122.6, 117.2, 117.1,
- ²⁰ 116.9, 116.2, 116.0, 115.4, 38.7; MS m/z (M⁺+Na): 849.9. HPLC method **B**, retention time: 4.405, Peak area: 85%.

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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- 19 To a mixture N-propargyl derivative of indole (1mmol) of CuI (10 mol%) in PEG-400 (5-7ml) was added benzyl azide (1.2 mmol) with stirring at room temperature. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was diluted by water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuo to get the crude product. The crude product was purified by column chromatography.
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Fe/Al pillard clay catalyzed solvent-free synthesis of bisindolylmethanes using diversly substituted indoles and carbonyl compounds.

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A fast, solvent free solid acid mediated synthetic strategy for the synthesis of bisindolylmethanes has been developed. The process is applicable to a wide range of substrate with different protecting group survival properties. Reusability of Fe/Al pillard clay for more than 5 cycles without significant loss of catalytic activity adds to the features of the reaction.



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